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66. (Twice Amended) A method for enhancing recovery of bone marrow using an immunostimulatory nucleic acid as compared to the absence of the immunostimulatory nucleic acid in a subject undergoing or having undergone cancer therapy, comprising:

administering to a subject undergoing or having undergone cancer therapy which damages the bone marrow an effective amount for enhancing the recovery of bone marrow of an immunostimulatory nucleic acid, comprising:

$$5' X_1 X_2CGX_3 X_4 3'$$

wherein C is unmethylated, wherein X_1X_2 and X_3X_4 are nucleotides.

REMARKS

Applicants have amended claims 42 and 66 to provide a frame of reference for the therapeutic methods. No new matter has been added.

The specification has been amended to update the related patent application information to indicate the patents that have been issued, to correct typographical errors which occurred in the brief description of the figures (the same errors were corrected previously in the parent patent application serial no. 08/960,774), to provide substitute sheets with legible copies of Tables 1-4, and to provide additional copies of replacement pages 38 and 47. No new matter has been added.

Interview with Examiner Martinell

Applicants express thanks to Examiner James Martinell for his courtesy in granting and conducting a personal Interview with Applicant Dr. Arthur Krieg and Applicants' representative on April 3, 2002. In the Interview, the rejections in view of 35 U.S.C. §112, second paragraph and first paragraph, were discussed. In particular, it was concluded that the rejection under 35 U.S.C. §112, second paragraph, could be overcome by including a frame of reference within claims 42 and 66. In response to the rejection under 35 U.S.C. §112, first paragraph, Applicants presented arguments that the specification as filed provided adequate guidance and examples demonstrating methods for administering, the times of frequency of administration, and dosages required to obtain those effects. Applicants also argued that the ability to translate the *in vitro* assays described in the specification into *in vivo* dosing parameters for oligonucleotides was known in the art at the time of the invention. Applicants presented several papers in the

antisense field which describe comparison of *in vitro* studies using antisense oligonucleotides to *in vivo* administration parameters. Examiner Martinell agreed that such documentation should be sufficient to overcome the rejections of record and requested that Applicants submit the references with a written response to the rejections.

Objection to the Disclosure

Replacement pages 38 and 47 previously filed with the response of March 7, 2001 have been objected to. The smaller font used in the replacement pages was not acceptable. Applicants have submitted new replacement pages 38 and 47 using larger font.

The Table on page 23 was not found to be completely legible because some of the characters were printed on top of others. New substitute sheet 23 is submitted herewith to provide a legible copy of the Table.

Rejection of Claims 42-70 Under 35 U.S.C. §112, Second Paragraph

Claims 42 and 66 have been rejected because they lack a frame of reference. As discussed with Examiner Martinell during the Interview, Applicants have now amended claims 42 and 66 to specifically add a frame of reference. The amendment does not narrow the scope of the claims. The amendment should be sufficient to overcome the rejection.

Rejection of Claims 42-75 and 76-98 Under 35 U.S.C. §112, First Paragraph

Claims 42-75 and 76-98 have been rejected under 35 U.S.C. §112, first paragraph, because of a "lack of guidance in the instant application as to the type of administration, the times or frequencies of administration, or the dosages required to obtain the desired effects".

As discussed in the Interview with Examiner Martinell, Applicants have previously pointed out guidance in the specification for administration methods and doses, e.g., methods for determining the stimulation index of a particular oligonucleotide to produce a particular cytokine are described in the specification. During the Interview, Applicants presented evidence that the *in vitro* assays described in the specification could be easily translated into *in vivo* dosing parameters for oligonucleotides by those of ordinary skill in the art. The correlation between *in vitro* assays for antisense oligonucleotides to that of *in vivo* dosing parameters for oligonucleotides was known in the art at the time the application was filed. The following

research articles published between 1991 and 1994 describe *in vivo* administration of antisense oligonucleotides.

Bayever et al., *Antisense Research and Development*, 3:383-390 (1993), attached as Exhibit 1, describes the systemic administration of an antisense oligonucleotide during a Phase I trial. The pharmacokinetics and clinical effects of the oligonucleotides were described in detail. The discussion concludes that "the recovery of up to approximately 60% of OL(1)p53 in urine during the 10-day infusion is consistent with the observations from preclinical studies in the rat (our unpublished observations, 1993) and monkey (Cornish et al., 1993)". (Page 388, second full paragraph in discussion.)

Cossum et al., *The Journal of Pharmacology and Experimental Therapeutics*, 269(1):89-94, attached as Exhibit 2, describes the pharmacokinetics of an antisense oligonucleotide after intradermal administration to rats. It is taught in the abstract that the "rate and characteristics of metabolism in the skin were similar to those observed in other tissues". The reference describes the tissue distribution and pharmacokinetics, metabolism and elimination of the oligonucleotide.

Agrawal et al., *PNAS*, 88:7595-7599 (1991), attached as Exhibit 3, describes an *in vivo* study in mice analyzing the pharmacokinetics, biodistribution and stability of oligonucleotides. It was concluded that a single intravenous or intraperitoneal administration resulted in the presence of oligonucleotide in most of the tissues studied for up to 48 hours.

The following three review articles were published in 1995 but described many studies performed prior to 1995.

Delivery Strategies for Antisense Oligonucleotide Therapeutics, S. Akhatar (Ed.) Vlassov et al., Chapter 5, *In Vivo* Pharmacokinetics of Oligonucleotides Following Administration by Different Routes, CRC Press Inc., Boca Raton, Florida, (1995), is attached as Exhibit 4. This book chapter describes *in vivo* administration of oligonucleotides by a variety of routes and the resulting pharmacokinetics. The authors concluded "oligonucleotides delivered by the above-mentioned administration routes reach animal organs in a biologically intact form". (Page 81, paragraph entitled "Conclusions".)

Agrawal et al., *Clinical Pharmacokinetics*, 28(1):7-16 1995, attached as Exhibit 5, is a review article describing *in vivo* administration and pharmacokinetics of oligonucleotides in monkeys, mice, rats and humans.

Crooke, Therapeutic Applications of Oligonucleotides, R.G. Landers Co., Austin, Texas, 1995, attached as Exhibit 6, Chapter 5 is a chapter from a book describing administration of phosphorothioate oligonucleotides. Beginning on page 70 of this chapter, *in vivo* pharmacokinetics are described.

In view of the teachings found in the specification as well as the state of the art at the time of the invention concerning the administration of antisense oligonucleotides for therapeutic purposes, one of ordinary skill in the art would have been enabled to practice the full scope of the claims.

In the Office Action, the Examiner indicated that the copy of Wooldridge, previously submitted, was not legible. Applicants submit herewith a legible, clean copy of Wooldridge et al.

Summary

Applicants have amended all of the claims as discussed in the Interview with Examiner Martinell and have presented the arguments discussed during the Interview. It is believed that all of the pending claims are now allowable. If the Examiner has any questions or comments, he is encouraged to contact Applicants' representative at the number listed below.

Respectfully submitted,

Krieg et al., Applicant(s)

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Docket No. C01039/70021
Date: June 26, 2002
X06/26/02